

Worldwide burden of gastric cancer in 2010 attributable to high sodium intake in 1990 and predicted attributable burden for 2030 based on exposures in 2010

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Abstract

Assessing the impact that patterns of Na intake may have on gastric cancer will provide a more comprehensive estimation of Na reduction as a primary prevention approach. We aimed to estimate the proportion of gastric cancer cases that are attributable to Na intake above the recommendation by the WHO (≤ 2 g/d) throughout the world in 2010, as well as expected values for 2030. Population attributable fractions (PAF) were computed for 187 countries, using Na intakes in 1990 and 2010 and estimates of the association between Na intake and gastric cancer, assuming a time lag of 20 years. Median PAF ranged from 10.1% in low to 22.5% in very high Human Development Index (HDI) countries in men ($P < 0.001$) and from 7.2 to 16.6%, respectively, among women ($P < 0.001$). An increase in median PAF until 2030 is expected in most settings, except for countries classified as low HDI, in both sexes. High Na intakes account for a large proportion of gastric cancer cases, and proportions are expected to increase in almost all of the countries. Intensified efforts to diminish Na intake in virtually all populations are needed to further reduce gastric cancer burden.

Key words: Sodium: Stomach neoplasms: Population attributable fractions: Predictions

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer death worldwide⁽¹⁾, despite the sustained decline in gastric cancer rates over the past several decades^(2,3). The apparent potential for an even greater decrease without specific interventions to control its main determinants contributes to the misperception that gastric cancer may no longer be an important public health concern, at least in more developed countries. However, in the most recent years, the relative declines were smaller in several settings, and a levelling off is already expected in a few countries⁽⁴⁾.

Na intake was one of the first exposures to be associated with gastric cancer^(5–7) and gastric pre-cancerous lesions^(8,9). Among all cancers, Na intake was found to be associated only with gastric cancer⁽⁷⁾, with high Na intake increasing the risk by approximately two-fold^(10,11).

Worldwide, increases in Na intake between 1990 and 2010 have been reported⁽¹²⁾, with consumption in 2010 exceeding the recommended levels in almost all countries. In fact, the

global mean Na intake (3.95 g/d) was nearly twice the WHO-recommended limit (2 g/d).

Given the high intakes of Na and the increasing trends observed at an international level, assessing the impact that these patterns of exposure may have on gastric cancer will provide data for a more comprehensive estimation of the impact of Na reduction as a primary prevention approach. Therefore, we aimed to estimate the population attributable fraction (PAF) for gastric cancer in 2010 that could be due to Na intake above the WHO recommendation throughout the world in 1990, and the corresponding figures expected for 2030 based on exposures in 2010.

Methods

PAF, that is, estimates of the proportion of gastric cancer cases that could be attributed to Na intake above the WHO recommendation (≤ 2 g/d)⁽¹³⁾, were computed for different countries.

Abbreviations: HDI, Human Development Index; PAF, population attributable fraction; RR, relative risk.

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We used country-specific data on Na intake and published estimates of the magnitude of the association between Na intake and gastric cancer. A time lag of 20 years was assumed on the basis of the similar magnitude of the association between Na intake and cancer⁽¹⁰⁾ and intestinal metaplasia⁽⁹⁾, which is in accordance with the model for the progression of gastric cancer proposed by Correa⁽⁸⁾.

Association between sodium intake and gastric cancer

We conducted a systematic review of meta-analyses to obtain estimates of the magnitude of association between Na intake and gastric cancer. A total of eighty-eight references were retrieved through a PubMed search, from inception to May 2015, and backward citation tracking. Full papers published in English, Portuguese, Spanish, French, Italian and Polish were evaluated. Articles not reporting the results of meta-analyses, of Na or salt intake as an exposure, of gastric cancer as an outcome or not performing a quantitative evaluation of the association between Na or salt intake and gastric cancer were excluded. Screening of reference lists and data extraction were accomplished independently by two researchers (B. P., C. C.), following a protocol defined *a priori*, and discrepancies were discussed until consensus or were resolved involving a third researcher (N. L.); five meta-analyses fulfilling the criteria were identified^(7,10,11,14,15). A detailed description of the published meta-analyses is provided in the online Supplementary Table S1 and results in Fig. 1.

Only one meta-analysis presented the results for Na (rather than salt) intake⁽⁷⁾, reporting a 1.14 increased risk *per* 1 g/d increment in Na intake.

Sodium intake

Mean levels of Na intake in 1990 and in 2010 by sex for 187 countries were retrieved from the Global Sodium Consumption Study⁽¹²⁾. It included published and unpublished data from 142 surveys of 24-h urinary Na and 103 of dietary Na conducted between 1980 and 2010 across sixty-six countries; a Bayesian model was used to convert dietary values into comparable 24-h urine values, and mean Na intake (g/d) was estimated without adjustment for non-urinary losses.

Calculation of population attributable fractions

We estimated the proportional reduction in gastric cancer incidence that would arise if exposure to Na corresponded to a counterfactual scenario, defined as the exposure that would result in the lowest population risk (e.g. a population in which no one exceeded the WHO reference value of ≤ 2 g/d of Na intake). We used the method proposed by Levin⁽¹⁶⁾ but applied to a continuous exposure⁽¹⁷⁾:

$$PAF = \frac{P(RR-1)}{P(RR-1)+1} = \frac{e^{(coefficient \times difference)} - 1}{e^{(coefficient \times difference)} + 1},$$

where *coefficient* is the logarithmic coefficient of the relative risk (RR) of the association between Na intake and gastric cancer *per* unit of increment in Na intake, and *difference* is the difference between the mean level of Na intake in each country and the WHO recommendation. From our systematic review, we obtained an estimate of the RR *per* unit of increment in Na intake, 1.14 *per* 1 g/d, equivalent to a logarithmic coefficient of 0.131.

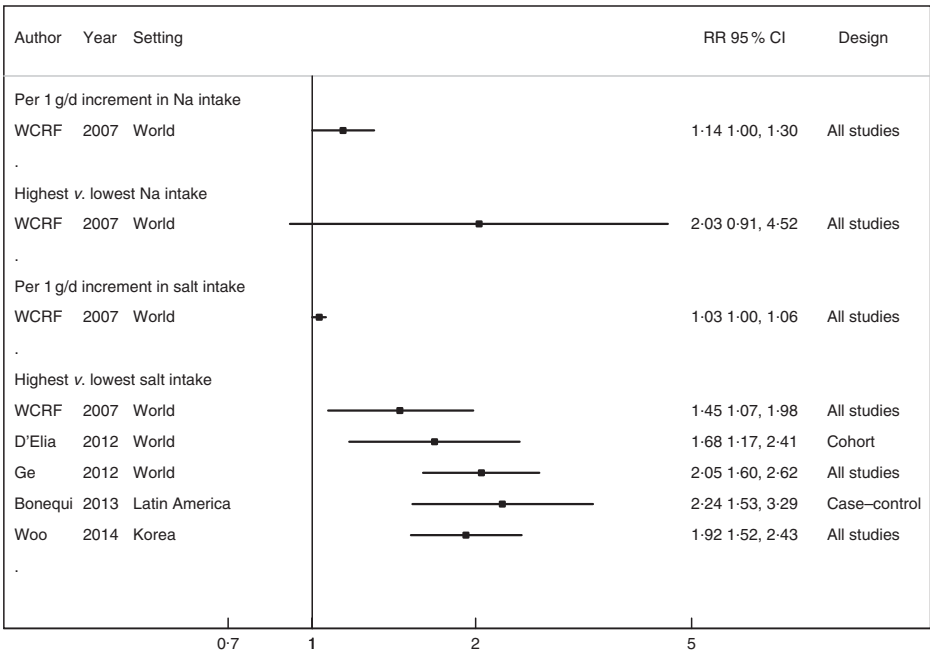


Fig. 1. Meta-analyses on the association between sodium or salt intake and gastric cancer. Meta-analyses identified through a PubMed search, from inception to May 2015, using the following expression: (gastric OR stomach) AND cancer AND (salt OR salted OR salty OR food OR sodium) AND ('systematic review' OR meta-analysis OR 'combined analysis' OR 'pooled analysis').



Estimates of PAF due to Na intake above the WHO recommendation in each country were computed for 2010 and 2030, for those with available Na intake estimates for 1990 and 2010, respectively. We multiplied each value by 100 to obtain PAF estimates in percentage. In countries where mean Na intake was below the WHO recommendation, PAF estimates were set to 0.0%.

PAF was treated as a continuous variable, and comparisons across sexes, time periods and regions were made using the Kruskal–Wallis test because of a non-normal distribution.

Results

There were wide geographical differences in PAF in 2010 and 2030 (Fig. 2 and online Supplementary Tables S2 and S3). Regardless of sex and time period, PAF estimates were higher in Asian regions, particularly in eastern and south-eastern Asia, and in Europe, mainly in central and eastern Europe. The lowest estimates of PAF were observed in Africa, especially in eastern Africa. Between 2010 and 2030, we observed, for most countries, an increase in the proportion of gastric cancer cases that could be attributed to Na intake above the WHO recommendation of ≤ 2 g/d in both sexes.

Fig. 3 depicts the distribution of PAF estimates according to the level of Human Development Index (HDI) of the country in 2010⁽¹⁸⁾. Significantly higher median PAF estimates were observed in men compared with women in both years in all geographic regions and across levels of HDI. Median PAF estimates increased with HDI ($P < 0.001$), ranging from 10.1% in those with low HDI to 22.5% in those with very high HDI in men and from 7.2 to 16.6%, respectively, in women. Countries for which no HDI evaluation was available presented median PAF similar to the ones observed in low-HDI countries (10.3% in men and 7.3% in women). For countries in all HDI groups, we observed a significant increase in the median proportion of cases attributable to high Na intake until 2030, except for countries classified as low HDI, in both sexes. Nevertheless, in all countries meeting the WHO recommendation for Na intake (≤ 2 g/d) in 1990, the PAF estimates remained zero in 2030, except for men in Jamaica (online Supplementary Tables S2 and S3).

Discussion

Na intake above the reference level recommended by the WHO (2 g/d) is responsible for an important share of the gastric cancer burden worldwide. The proportion of gastric cancer cases that can be attributed to high Na intake differs substantially across countries with different levels of development, as expected, due to regional differences in Na intake.

To our knowledge, this is the first study computing the proportion of gastric cancer cases that could be attributed to Na intake above the WHO recommendation (≤ 2 g/d), at the international level. Previous analyses addressing the global effect of Na intake were mostly focused on CVD, via hypertension⁽¹⁹⁾. However, at the regional level, one study has performed a similar analysis in the UK⁽²⁰⁾. Compared with our study, higher values in men (30.9 *v.* 20.5%) and lower values in women (12.1 *v.* 14.6%) were reported for gastric cancer cases

diagnosed in 2010 in the UK. A few differences in the way the analysis was conducted may account for these disparities – namely, the use of a lower RR estimate (1.08 *v.* 1.14 *per* 1 g/d) and a higher recommended maximum level for Na intake (2.4 *v.* 2 g/d) contributed to lower estimates of PAF. On the contrary, the higher mean Na intakes (4.40 *v.* 3.75 g/d in men and 3.24 *v.* 3.21 g/d in women) used in their calculations led to higher estimates of PAF. Nevertheless, they assumed a latent period based on the duration of follow-up in the two studies contributing to the pooled RR value used in their study, which was shorter than the one we presumed (10 *v.* 20 years), precluding a direct comparison between estimates. Since this study was published, one meta-analysis of prospective studies⁽¹⁰⁾, including the previous two and five additional ones, found relatively stronger associations in those with a follow-up of 10 or more years. In addition, we considered the results of a meta-analysis addressing the association between Na consumption and intestinal metaplasia, showing a magnitude of the association similar to the one observed for gastric cancer as an end point⁽⁹⁾. Taking into account the model for the progression of gastric cancer proposed by Correa⁽⁸⁾, which shows a 30–50-year duration in the process between gastric atrophy to cancer, the 20 years time lag assumed in our analysis seems to be more plausible, which is expected to contribute to more accurate estimates of PAF in our study.

Our results show variation according to sex, with 18 and 14% of gastric cancer cases in 2010 being attributed to high Na intake in men and women, respectively. These differences were observed across countries with different levels of HDI and regardless of the time period, and they mainly reflect the difference in mean Na intakes observed between sexes. Nevertheless, the accuracy of our estimates of PAF could have been improved if sex-specific summary RR were also available, but studies providing information for gastric cancer risk associated with Na intake stratified by sex are scarce⁽⁷⁾, and no significant differences were reported in subgroup analyses for the relationship between categories of Na intake and risk of gastric cancer^(10,11).

The burden of gastric cancer attributable to Na intake above the WHO recommendation also differs according to the socio-economic status at country level, which is higher in more developed countries compared with those less developed. However, much lower gastric cancer PAF are observed in countries with low HDI and there was no meaningful variation between 2010 and 2030, which is in accordance with Na intakes near the recommended level in these settings⁽¹²⁾ and relatively stable levels of intake between 1990 and 2010, respectively.

Following the marked differences in Na intake identified across regions, Asia presented the highest PAF in both periods due to the peak levels of Na intake observed in this continent in 1990 and the largest increase until 2010. On the contrary, African countries presented the lowest mean Na intakes by sex, with virtually no changes between 1990 and 2010, and therefore the lowest PAF estimates were observed in this setting. Nevertheless, the attributable gastric cancer burden in some geographic regions may be underestimated because of less reliable estimates of Na intake. Although the surveys used to estimate national Na intakes covered 74% of the global adult population, only 35% were nationally representative⁽¹²⁾.

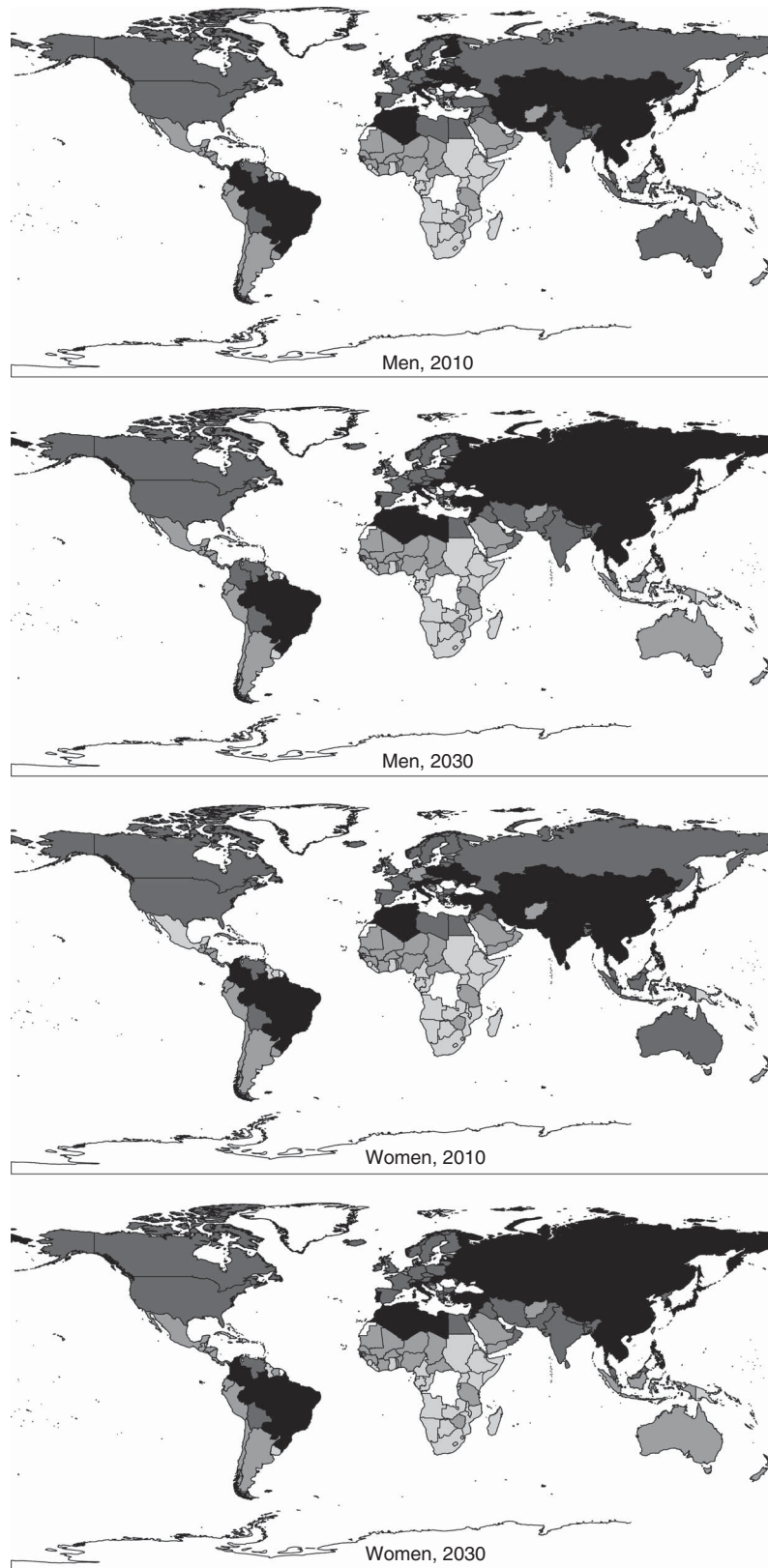


Fig. 2. Estimates of population attributable fractions (%) for gastric cancer in 2010 and 2030 (quartiles of the distributions in 2010 and in 2030 were used as cut-offs) as a result of sodium intake above the WHO recommendation (≤ 2 g/d) in 187 countries by sex in 1990 and 2010, respectively. Men 2010: □, no data; ■, 0.0–10.3; ■, 10.4–17.8; ■, 17.9–23.1; ■, 23.2–37.8. Men 2030: □, no data; ■, 0.0–10.9; ■, 11.0–19.4; ■, 19.5–25.9; ■, 26.0–43.1. Women 2010: □, no data; ■, 0.0–7.3; ■, 7.4–14.3; ■, 14.4–18.7; ■, 18.8–33.2. Women 2030: □, no data; ■, 0.0–7.6; ■, 7.7–15.9; ■, 16.0–22.0; ■, 22.1–38.4.

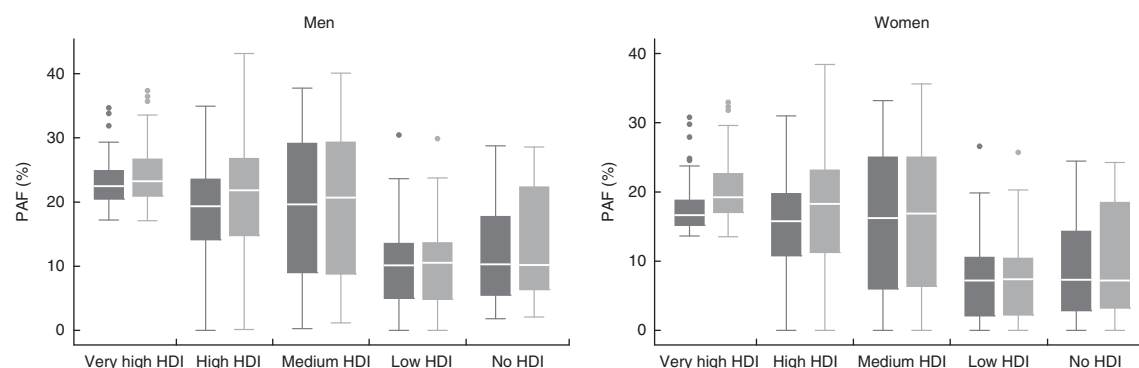


Fig. 3. Estimates of population attributable fractions (PAF) for gastric cancer in 2010 (■) and 2030 (□) as a result of sodium intake above the WHO recommendation (≤ 2 g/d) in 187 countries by sex in 1990 and 2010, respectively, according to Human Development Index (HDI) in 2010. In each group of countries, the white line represents the median, the box represents the interquartile range (IQR), the upper and lower limits represent values up to 1.5 times the IQR and the dots represent outliers of the PAF distribution, respectively. HDI distribution in 2010 was retrieved from the Human Development Report, 2010⁽¹⁸⁾: forty, forty-three, forty-three and forty-two countries were classified as very high, high, medium and low HDI, respectively, and no evaluation was available for nineteen countries: Antigua and Barbuda, Bhutan, Cuba, Dominica, Eritrea, Grenada, Iraq, Kiribati, North Korea, Lebanon, Marshall Islands, Oman, Palestine, Saint Lucia, Saint Vincent and the Grenadines, Samoa, Seychelles, Somalia, Vanuatu.

Differences in mean Na intakes across countries from 1990 to 2010 represent the net result of potentially large reductions in Na intakes over time⁽⁶⁾, consistent with changes in the traditional methods of food preservation made possible by the widespread availability of domestic refrigeration, and the recent increase in the global consumption of highly processed foods⁽²¹⁾, countering or even reversing these historical associations between modernisation and declining Na intakes. Therefore, upward trends in Na intakes have been observed worldwide⁽¹²⁾, which explain the predicted increase in PAF from 2010 to 2030 in most settings. Nevertheless, in the few countries where a decline in PAF was observed during this period, this may be insufficient to overcome the increase in the number of cases due to population growth and ageing⁽²²⁾. However, accurate estimates of the future attributable disease burden can only be obtained when predictions take into account the latest observed trends in gastric cancer incidence and the projected changes in population structure.

The assumptions underlying valid estimation of PAF include a causal relationship between exposure and disease and that unbiased and free from confounding RR estimates are available for the relation between the exposure and the outcome. Regarding the evidence of a causal role of Na in gastric carcinogenesis, this has already been pointed out as a major component of the causal mechanisms leading to gastric cancer⁽⁸⁾. In 1997, the World Cancer Research Fund classified Na as a probable cause of gastric cancer⁽²³⁾, which was further confirmed in its updated report in 2007⁽⁷⁾. This evaluation was based on cohort, case-control and ecological studies conducted in various parts of the world showing a consistent association between Na intake and gastric cancer, and also presented data regarding a dose-response relationship and the effect on pre-malignant conditions. Most of the studies included in these reviews of the evidence presented RR estimates adjusted for sex, age, *Helicobacter pylori* infection status, smoking status and other dietary factors – namely, the consumption of fruits and vegetables. Although residual confounding cannot be ruled out, it is unlikely that control for the effects of potentially major

confounders has not been accomplished. For the present study, we used the best available evidence on the association between Na intake and gastric cancer, obtained from the dose-response meta-analysis published in the second expert report⁽⁷⁾, which included cohort and case-control studies. However, summary estimates are higher if only retrieved only from case-control studies (RR 1.18 *per* 1 g/d increment in Na intake; 95% CI 1.02, 1.38⁽⁷⁾). This may have contributed to a conservative bias in our estimates of PAF, although not compromising the comparison across regions. In addition, no significant differences in the association between Na intake and gastric cancer according to tumour location or histological type have been described⁽⁷⁾, contributing to the accuracy of our estimates of the gastric cancer burden attributable to high Na intake.

The estimates of Na intake used in our study came from systematically identified and extracted data from around the world on both urinary and dietary Na, including many sources with previously unavailable data and showing a good agreement between the two metrics, as well as data from the Food Balance Sheets of the Food and Agriculture Organization of the United Nations⁽²⁴⁾, which captures the annual availability of food for human consumption on the basis of reported local production, imports and exports, at a country level. However, primary data sources were limited or missing in many countries, and the model reported by Powles *et al.*⁽¹²⁾ used information from neighbouring countries, taking into account similarities in country-level covariates. According to the 95% uncertainty intervals computed for Na intake in each country, precision decreases from very high to low-HDI countries, which may have contributed to inaccuracies in the country-specific PAF estimates. However, given the marked differences between these two levels of HDI, with very high presenting a median PAF that is double of the one observed in low-HDI countries, little effect may arise even if underestimation may be occurring in low-HDI settings and overestimation may be found in the very high settings. In addition, this is unlikely to compromise the definition of general patterns, particularly with respect to differences across sexes and between 2010 and 2030.

Gastric cancer is currently interpreted as a multifactorial complex disease, and therefore different sets of causal mechanisms leading to its occurrence may coexist⁽²⁵⁾. Under this assumption, the same exposure (e.g. Na intake) may contribute to the incidence of gastric cancer when occurring together with different sets of other exposures (e.g. *H. pylori* infection or *H. pylori* infection and fruit consumption or *H. pylori* infection and smoking). Although the different causal mechanisms potentially leading to gastric cancer are not known, the estimated PAF reflect a scenario where Na intake is within the range recommended by the WHO, and therefore affecting all of the possible pathways to cancer, regardless of the remaining exposures that take part in those causal mechanisms. Therefore, our results provide information on the importance of Na as a cause of gastric cancer, and show how improvements in Na-reduction strategies may gradually contribute to decrease the burden of gastric cancer.

In conclusion, high Na intake accounts for a large proportion of gastric cancer cases, and this proportion is expected to increase in the next few decades in almost all countries. Intensified efforts to reduce Na intake in virtually all populations are needed to further decrease the burden of gastric cancer.

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B. P. formulated the research question; B. P. and N. L. designed the study; B. P., S. B., C. C., A. F. and S. M. carried out the study; B. P. and C. C. analysed the data; and B. P. and N. L. wrote the article. All authors read and approved the final version of the manuscript.

The authors declare that they have no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit <http://dx.doi.org/doi:10.1017/S0007114516002518>

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